

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

**EP 0 520 555 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
01.09.1999 Bulletin 1999/35

(21) Application number: 92201770.2

(22) Date of filing: 17.06.1992

(51) Int. Cl.<sup>6</sup>: **C07D 453/02**, C07D 487/08,  
C07D 471/08, A61K 31/435,  
A61K 31/40, A61K 31/55  
// (C07D487/08, 209:00,  
209:00), (C07D487/08, 209:00,  
205:00), (C07D471/08, 221:00,  
209:00), (C07D471/08, 223:00,  
221:00), (C07D487/08, 223:00,  
223:00)

(54) **Azabicyclic compounds, pharmaceutical compositions containing them and their use in therapy**

Azabicyclische Verbindungen, diese enthaltende pharmazeutische Zubereitungen und ihre  
therapeutische Verwendung

Composés azabicycliques, compositions pharmaceutiques les contenant et leur utilisation  
thérapeutique

(84) Designated Contracting States:  
CH DE FR GB IT LI NL

(30) Priority: 24.06.1991 GB 9113567

(43) Date of publication of application:  
30.12.1992 Bulletin 1992/53

(73) Proprietor:  
MERCK SHARP & DOHME LTD.  
Hoddesdon Hertfordshire EN11 9NU (GB)

(72) Inventors:  
• Baker, Raymond  
Much Hadham, Hertfordshire (GB)  
• Swain, Christopher J.  
Duxford, Cambridge (GB)  
• Teall, Martin R.  
Standon, Nr. Ware, Hertfordshire (GB)

• Williams, Brian J.  
Great Dunmow, Essex (GB)

(74) Representative:  
Barrett-Major, Julie Diane et al  
Merck & Co., Inc.  
European Patent Department  
Terlings Park  
Eastwick Road  
Harlow Essex CM20 2QR (GB)

(56) References cited:  
WO-A-90/05729

Remarks:

The file contains technical information submitted  
after the application was filed and not included in  
this specification

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

**EP 0 520 555 B1**

## Description

[0001] This invention relates to a class of azabicyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azabicyclic ring system substituted by an arylmethoxy or arylmethylthio moiety and by a benzyl- or cycloalkyl-methyl moiety, their preparation, formulations thereof and their use in medicine.

[0002] The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub>

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH<sub>2</sub>

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH<sub>2</sub>

[0003] For example, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al.*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al.*, J. Med Chem, (1982) 25 1009) and in arthritis [Levine *et al.* in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al.* in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al.* Elsevier Scientific Publishers, Amsterdam (1987) page 85]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al.* "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad *et al.* "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne *et al.* in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al.* Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz *et al.* Science (1988) 241 1218-21 and Kimball *et al.* J. Immunol. (1988) 141 (10) 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al.*, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing  $\beta$ -amyloid-mediated neurodegenerative changes [Yankner *et al.* Science (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome.

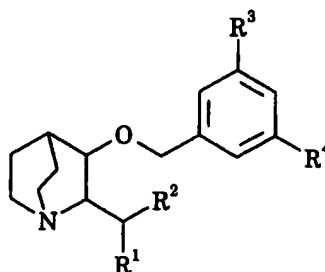
[0004] Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod *et al.*, poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July 1992, in press].

[0005] In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

[0006] WO-A-90/05729 describes *inter alia* a class of *cis*-3-[cyclic]methylamino-2-[( $\alpha$ -substituted)-aryl(methyl)quinolidine] compounds which are stated to be useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. There is, however, no disclosure or suggestion in WO-A-90/05729 of the arylmethoxy- or arylmethylthio-substituted azabicyclic derivatives provided by the present invention.

[0007] We have now found a further class of non-peptides which are potent antagonists of tachykinin.

[0008] The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

- R<sup>1</sup> represents unsubstituted phenyl or phenyl substituted by methoxy;  
 R<sup>2</sup> represents benzyl or cyclohexyl; and  
 R<sup>3</sup> and R<sup>4</sup> independently represent methyl or trifluoromethyl.

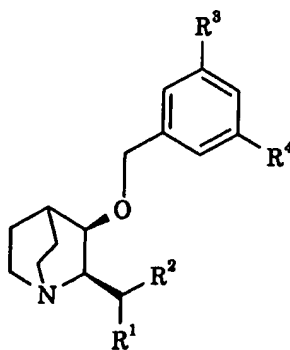
[0009] It will be appreciated that, except in the case of a quaternary ammonium salt, the nitrogen atom in the azabicyclic ring system will carry a lone pair of electrons. Especially preferred is when R<sup>3</sup> and R<sup>4</sup> are identical.

[0010] A particularly preferred subgroup of compounds of formula (I) are compounds wherein R<sup>3</sup> and R<sup>4</sup> are identical and are methyl or trifluoromethyl, more preferably trifluoromethyl.

[0011] The compounds according to the invention have at least two asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. In particular, the relative orientation of the 2- and 3-substituents on the azabicyclic ring system in formula (I) above may give rise to *cis* and *trans* diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

[0012] It is believed that of the *cis* diastereomers, tachykinin receptor antagonist activity preferentially resides in the 2S,3S diastereomer, whereas of the *trans* diastereomers, activity preferentially resides in the 2R,3S diastereomers. Thus, it is believed that S stereochemistry at the 3-position of the azabicyclic is crucial to tachykinin receptor antagonist activity.

[0013] A particular sub-class of compounds according to the invention is represented by the compounds of formula (IIA), and pharmaceutically acceptable salts thereof:

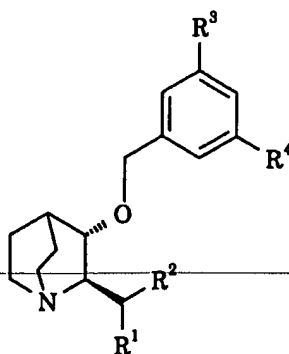


(IIA)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as previously defined.

[0014] A further sub-class of compounds according to the invention is represented by the compounds of formula (IIB),

and pharmaceutically acceptable salts thereof:



(IIB)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as previously defined.

[0015] For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, oxalic acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

[0016] The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

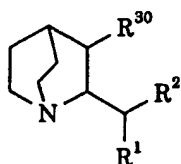
[0017] The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

[0018] The compounds of the present invention are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurode-

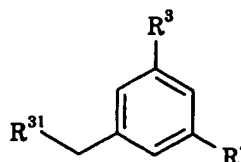
generative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as diabetic or peripheral neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy, and neuralgia; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder-function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. Thus, the present invention further provides a compound for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound or composition of this invention.

[0019] In the treatment of conditions involving actions of tachykinins released physiologically in response to noxious or other stimuli, a suitable dosage level is about 0.01 to 500 mg/kg per day, such as 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

[0020] The compounds according to the invention may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

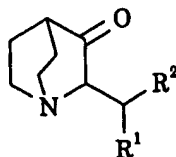
wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined for formula (I) above, and one of  $R^{30}$  and  $R^{31}$  represents a leaving group and the other of  $R^{30}$  and  $R^{31}$  represents OH; in the presence of a base.

[0021] Suitably,  $R^{31}$  represents a leaving group and  $R^{30}$  represents OH.

[0022] Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

[0023] The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the range of -5 to 25°C, preferably about 0°C. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide and potassium hydride. Suitably, potassium bis(trimethylsilyl)amide is used.

[0024] The intermediates of formula (III) above wherein  $R^{30}$  is OH may be prepared by reduction of the corresponding ketone of formula (V)



(V)

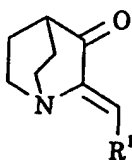
wherein  $R^1$  and  $R^2$  are as defined above. Suitable reducing agents will be readily apparent to a person skilled in the art and include, for example, metal hydrides, such as lithium aluminium hydride and sodium borohydride, or hydrogen in the presence of a catalyst, such as noble metal catalyst, e.g. palladium on charcoal. The reaction is conveniently effected in a suitable solvent. Suitable solvents will depend on the nature of the reducing agent employed and will be readily apparent to those skilled in the art.

[0025] Intermediates of formula (II) wherein  $R^{30}$  is OH having *cis* stereochemistry may preferably be prepared from the corresponding ketones via a selective reduction using a suitable reducing agent such as a lithium aluminium hydride or a substituted borohydride such as triethylborohydride.

[0026] Intermediates of formula (III) wherein  $R^{30}$  is OH having *trans* stereochemistry may be obtained selectively via a procedure involving non-selective reduction of the corresponding ketone, for example using sodium in an aromatic hydrocarbon solvent, e.g. toluene, preferably in the presence of an alcohol, e.g. iso-propyl alcohol, to give a mixture of *cis* and *trans* isomers, followed by selective oxidation of the *cis* isomer using a ketone in the presence of a base (Oppenauer oxidation). Suitable ketones include acetone, methyl ethyl ketone, cyclohexanone and, preferably, benzophenone. Suitable bases include alkali metal hydrides, e.g. potassium hydride.

[0027] Intermediates of formula (III) wherein  $R^{30}$  is a leaving group may be prepared from compounds of formula (III) wherein  $R^{30}$  is OH, for example, by reaction with a thionyl halide, a mesyl halide or a tosyl halide.

[0028] Ketones of formula (V) may be prepared from intermediates of formula (VIII)



(VIII)

wherein  $R^1$  is as defined above, by reaction with a compound of formula  $R^2MgHal$ , where Hal represents halo such as chloro, bromo or iodo.

[0029] Intermediates of formula (VIII) may be prepared by the procedures described in *J. Org. Chem.*, 1974, 39, 3511; or by methods analogous thereto.

[0030] Where they are not commercially available, the intermediates of formula (IV), (VI) and (VII) above may be prepared by conventional procedures which will be readily apparent to one skilled in the art.

[0031] Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

[0032] The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, intermediate alcohols of formula (III), wherein  $R^{30}$  is OH, may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. The diastereomeric alcohols can then be used to prepare optically pure compounds of formula (I).

[0033] During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W.

Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[0034] The following Examples illustrate the preparation of compounds according to the invention.

5 EXAMPLE 1: 3-[(3,5-Dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane

a) 2-(1,2-Diphenylethyl)-3-oxo-1-azabicyclo[2.2.2]octane

[0035] To a stirred solution of 2-benzylidene-3-oxo-1-azabicyclo[2.2.2]octane (10g) in diethyl ether (200ml) at -10°C under a nitrogen atmosphere was added a solution of 2M-benzylmagnesium chloride (30ml, in tetrahydrofuran, 60mmol) and diethyl ether (100ml). The solution was stirred at -10°C for 30 minutes and at ambient temperature for 16h. A saturated solution of aqueous ammonium chloride (200ml) was carefully added and the product extracted into ethyl acetate. The organic phase was dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was chromatographed on a column containing silica gel 60 (220-440 mesh ASTM) eluting with mixtures of 30%, 50% and 70% ethyl acetate in petroleum ether (bp 60-80°C). 2-(1,2-diphenylethyl)-3-oxo-1-azabicyclo[2.2.2]octane was obtained as 1:1 mixture of stereoisomers by evaporating the appropriate fractions.

b) 2-(1,2-Diphenylethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane

[0036] To a solution of the product of Example 1a, (3.1g; 1:1 mixture of diastereomers) in tetrahydrofuran (50ml) at -78°C was added a solution of 1M-lithium aluminium hydride (10.16ml, in diethyl ether). After the solution had stirred at -78°C for 2h, water (3ml) was added followed by aqueous 2M-sodium hydroxide (3ml) and water (6ml). When at room temperature, diethyl ether was added and the mixture filtered through Hyflo supercel. The ethereal phase of the filtrate was washed with water (2 x 30ml), brine (30ml) and dried (MgSO<sub>4</sub>). After removal of the solvent *in vacuo* the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (bp 60-80°C) (1:1) followed by methanol/ethyl acetate (1:50) to give the title compound as a mixture of stereoisomers.

c) 3-[(3,5-Dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt

[0037] To a solution of alcohol (Example 1b, 0.78g, 1:1 mixture of stereoisomers) was added 0.5M-potassium hexamethyldisilazide (5.84ml, in toluene). After 1h, 3,5-dimethylbenzyl bromide (0.58g) was added for 3h. The solution was evaporated to dryness after a further 3h, and the residue partitioned between dichloromethane and water. The organic phase was dried (MgSO<sub>4</sub>), evaporated and purified by column chromatography on silica gel eluting with petroleum ether (bp 60-80) containing increasing amounts of ethyl acetate (50% to 100%) and then methanol/ethyl acetate (15:85) to give a single diastereomer of the title compound. This was crystallised by addition of oxalic acid (72mg) in propan-2-ol and diethyl ether to give 3-[(3,5-dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt isomer A mp 64-66°C. <sup>1</sup>H NMR (DMSO, 360MHz) δ 7.2-6.6 (13H, m, aryl), 4.6 (1H, d, J = 16.0Hz, OCH<sub>A</sub>H<sub>B</sub>), 4.4 (1H, d, J = 16.0Hz, OCH<sub>A</sub>H<sub>B</sub>), 3.5 (1H, m, OCHCH), 3.3 (1H, m, NCH<sub>A</sub>H<sub>B</sub>), 2.99 (1H, dd, NCHCH), 2.8-2.60 (5H, m, NCH<sub>A</sub>H<sub>B</sub>, NCH<sub>2</sub>, PhCH<sub>2</sub>), 2.4 (1H, m, PhCHCH<sub>2</sub>), 2.3 (6H, s, CH<sub>3</sub>, CH<sub>3</sub>), 2.25 (1H, m, bridgehead CH), 1.9 (1H, m, NCH<sub>2</sub>CH<sub>A</sub>H<sub>B</sub>), 1.65 (1H, m, NCH<sub>2</sub>CH<sub>A</sub>H<sub>B</sub>), 1.46-1.22 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>); Found C, 71.09; H, 6.84; N, 2.51. C<sub>30</sub>H<sub>35</sub>NO. C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>.0.3H<sub>2</sub>O requires C, 71.19; H, 6.86; N, 2.67. m/e (EI) 425 (M<sup>+</sup>), (Cl<sup>+</sup>) 426 (M+H), (Cl<sup>-</sup>) 424 (M-H).

[0038] Chromatographic separation performed above (Example 1c) also yielded isomer B, which was recrystallized as an oxalate salt from ethanol/diethyl ether to give 3-[(3,5-dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt isomer B; m.p. 128-130°C; C<sub>30</sub>H<sub>35</sub>NO. C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>.H<sub>2</sub>O requires C, 72.03; H, 7.36; N, 2.62. Found: C, 71.96; H, 7.30; N, 2.62%.

[0039] The product of Example 1a was crystallized from diethyl ether. The mother liquor (enriched in one diastereomer) was reduced according to the procedure described (Example 1b) an alkylated (Example 1c) to give 3-[(3,5-dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate isomer C m.p. 55-58°C; C<sub>30</sub>H<sub>35</sub>NO.1.5 (C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).H<sub>2</sub>O requires C, 68.49; H, 6.96; N, 2.42. Found: C, 68.84; H, 7.01; N, 2.60%.

[0040] The following Examples were prepared similarly.

EXAMPLE 2: 3-(3,5-bis-Trifluoromethylphenyl)methyloxy-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt

[0041] The title compound was prepared from 2-(1,2-diphenylethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane (Example 1b) using 3,5-bis-trifluoromethylbenzyl bromide to give:

Isomer A, m.p. 150-153°C; C<sub>30</sub>H<sub>29</sub>NOF<sub>6</sub>. C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>.0.5H<sub>2</sub>O requires C, 60.75; H, 5.09; N, 2.21. Found: C, 60.84; H,



4.85; N, 2.17%.

Isomer B m.p. 175-177°C; C<sub>30</sub>H<sub>29</sub>NOF<sub>6</sub>·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>·0.75H<sub>2</sub>O requires C, 60.32; H, 5.14; N, 2.20. Found: C, 60.15; H, 5.22; N, 2.37%.

Isomer C m.p. 146-148°C; C<sub>30</sub>H<sub>29</sub>NOF<sub>6</sub>·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>·0.25H<sub>2</sub>O requires C, 60.75; H, 5.10; N, 2.21. Found: C, 60.44; H, 5.11; N, 2.14%.

EXAMPLE 3: 3-(3,5-bis-Trifluoromethylphenyl)methoxy-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane hydrogen oxalate salt

[0042]

Isomer A m.p. 83°C; C<sub>31</sub>H<sub>31</sub>NO<sub>2</sub>F<sub>6</sub>·1.3 (C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 59.29; H, 4.97; N, 2.05. Found: C, 59.16; H, 5.12; N, 2.12%.

EXAMPLE 4: 3-(3,5-bis-Trifluoromethylphenyl)methoxy-2-[1-(1-(3-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane hydrogen oxalate salt

[0043]

Isomer A m.p. 179-180°C; C<sub>31</sub>H<sub>31</sub>NO<sub>2</sub>F<sub>6</sub>·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires C, 60.64; H, 5.09; N, 2.14. Found: C, 60.28; H, 5.33; N, 2.16%.

Isomer B m.p. 148-151°C; C<sub>31</sub>H<sub>31</sub>NO<sub>2</sub>F<sub>6</sub>·3.6 (C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>)·0.25CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub> requires C, 51.74; H, 4.35; N, 1.58. Found: C, 51.34; H, 4.77; N, 1.94%.

EXAMPLE 5: 3-(3,5-Bis(trifluoromethyl)phenyl)methoxy-2-(α-cyclohexylbenzyl)-1-azabicyclo[2.2.2]octane oxalate hemihydrate

[0044]

a) 2-(α-cyclohexylbenzyl)-3-oxo-1-azabicyclo[2.2.2]octane

The title compound as a mixture of diastereomers was prepared in a manner analogous to that described in Example 1a using cyclohexylmagnesium chloride.

b) Using conditions analogous to those described in Example 1b and c the product of Example 5a was reduced and alkylated (with 3,5-bis(trifluoromethyl)benzyl bromide to give 3-(3,5-bis(trifluoromethyl)phenyl)methoxy-2-(α-cyclohexylbenzyl)-1-azabicyclo[2.2.2]octane oxalate hemihydrate, mp 119-121°C. Found: C, 59.33; H, 5.67; N, 2.22. C<sub>29</sub>H<sub>33</sub>NOF<sub>6</sub>·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>·0.5(H<sub>2</sub>O) requires C, 59.61; H, 2.24; N, 5.89%. m/e (Cl<sup>+</sup>) = 526 (M+H), (Cl<sup>-</sup>) = 524 (M-H).

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 6A Tablets containing 1-25mg of compound

[0045]

Amount mg			
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

**EXAMPLE 6B Tablets containing 26-100mg of compound****[0046]**

5

10

15

Amount mg			
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

20

[0047] The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

**EXAMPLE 7 Parenteral injection****[0048]**

25

30

35

Amount mg	
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for injection	to 1ml

40

[0049] The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

**EXAMPLE 8 Topical formulation****[0050]**

45

50

Amount mg	
Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

55

[0051] The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

SUBSTANCE P ANTAGONISM ASSAYA. Receptor Expression in Monkey Kidney Cell Line (COS)

- 5 [0052] To express the cloned human neurokinin-1- receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+ (trademark, STRATAGENE, La Jolla, CA, USA)) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electro-
- 10 poration in 800  $\mu$ l of transfection buffer (135 mM NaCl, 1.2 mM  $\text{CaCl}_2$ , 1.2 mM  $\text{MgCl}_2$ , 2.4 mM  $\text{K}_2\text{HPO}_4$ , 0.6 mM  $\text{KH}_2\text{PO}_4$ , 10 mM glucose, 10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulphonic acid (HEPES) pH 7.4) at 260 V and 950  $\mu$ F using the IBI GENEZAPPER (trademark IBI, New Haven, CT, USA). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY, USA) in 5%  $\text{CO}_2$  at 37°C for three days before the binding assay.

15 B. Stable Expression in Chinese Hamster Ovarian Cell Line

- [0053] To establish a stable cell line expressing cloned human NK1R, the cDNA was subcloned into the vector pRc-CMV (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800  $\mu$ l of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950  $\mu$ F using the IBI GENE-
- 20 ZAPPER (IBI). The transfected cells were incubated in CHO media [10% fetal calf serum, 100 U/ml penicillin-streptomycin, 2 mM glutamine, 1/500 hypoxanthinethymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS, USA), 0.7 mg/ml G418 (GIBCO)] in 5%  $\text{CO}_2$  at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

25 C. Assay Protocol using COS or CHO

- [0054] The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of  $^{125}\text{I}$ -sub-
- 30 stance P ( $^{125}\text{I}$ -SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavellette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM  $\text{MnCl}_2$ , 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200  $\mu$ l of the cell suspension would give rise to about 10,000 cpm of specific  $^{125}\text{I}$ -SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200  $\mu$ l of cells were added to a tube con-
- 35 taining 20  $\mu$ l of 1.5 to 2.5 nM of  $^{125}\text{I}$ -SP and 20  $\mu$ l of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1% polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM  $\text{MnCl}_2$ , 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

- 40 [0055] The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of  $\text{IP}_3$ . CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 5  $\mu$ Ci of  $^3\text{H}$ -myoinositol in 1 ml of media per well by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 10 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3nM
- 45 to activate the human NK1R. After 30 min of incubation at 37°C, the medium is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with  $\text{CHCl}_3$ /methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated
- 50 by beta counter.

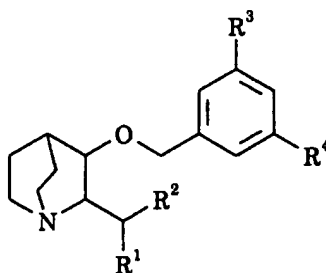
[0056] The data in Table 1 were obtained for compounds of formula (I):

TABLE 1

SUBSTANCE P ANTAGONISM RESULTS	
Compound of Ex #	IC <sub>50</sub> @ NK1R (nM)
1 : ISOMER A	2.4
1 : ISOMER B	1.8
1 : ISOMER C	>100
2 : ISOMER A	4.5
2 : ISOMER B	6.3
2 : ISOMER C	>100
3 : ISOMER A	3.0
4 : ISOMER A	10.0
4 : ISOMER B	1.8
5	3.0

## Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R<sup>1</sup> represents unsubstituted phenyl or phenyl substituted by methoxy;  
 R<sup>2</sup> represents benzyl or cyclohexyl; and  
 R<sup>3</sup> and R<sup>4</sup> independently represent methyl or trifluoromethyl.

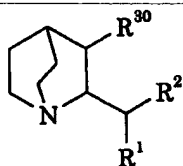
2. A compound as claimed in claim 1 wherein R<sup>3</sup> and R<sup>4</sup> are both trifluoromethyl.
3. A compound as claimed in claim 1 selected from
- 3-[(3,5-dimethylphenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane;  
 3-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane;  
 3-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane;  
 3-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-[1-(1-(3-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane;

clo[2.2.2]octane;

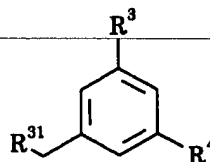
3-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-( $\alpha$ -cyclohexylbenzyl)-1-azabicyclo[2.2.2]octane;

and salts thereof.

4. A compound as claimed in any one of the preceding claims for use in therapy.
5. A process for the preparation of a compound as claimed in any one of claims 1 to 3 which process comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



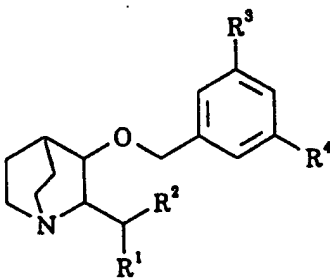
(IV)

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined for formula (I), and one of  $R^{30}$  and  $R^{31}$  represents a leaving group and the other of  $R^{30}$  and  $R^{31}$  represents OH; in the presence of a base.

6. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 3 in association with a pharmaceutically acceptable carrier or excipient.
7. The use of a compound as claimed in any of claims 1 to 3 for the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins.

#### Patentansprüche

1. Eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz davon:



(I)

worin

$R^1$  unsubstituiertes Phenyl oder durch Methoxy substituiertes Phenyl bedeutet,  
 $R^2$  Benzyl oder Cyclohexyl bedeutet und  
 $R^3$  und  $R^4$  unabhängig Methyl oder Trifluormethyl bedeuten.

2. Eine wie in Anspruch 1 beanspruchte Verbindung, worin  $R^3$  und  $R^4$  beide Trifluormethyl sind.

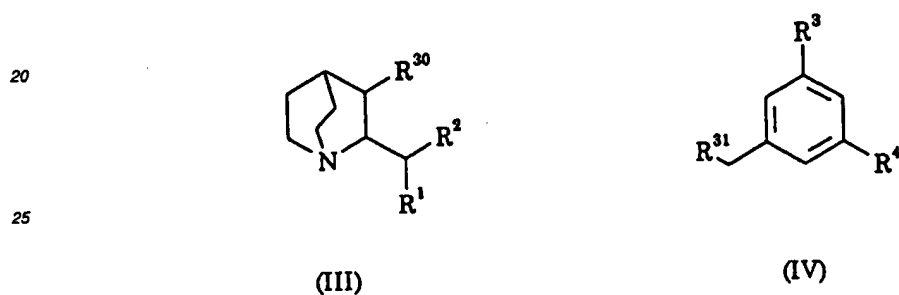
3. Eine wie in Anspruch 1 beanspruchte Verbindung, ausgewählt aus

- 5 3-[(3,5-Dimethylphenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octan,  
 3-[(3,5-Bistrifluormethylphenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octan,  
 3-[(3,5-Bistrifluormethylphenyl)methoxy]-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-azabi-  
 cyclo[2.2.2]octan,  
 3-[(3,5-Bistrifluormethylphenyl)methoxy]-2-[1-(1-(3-methoxyphenyl)-2-phenyl)ethyl]-1-azabi-  
 cyclo[2.2.2]octan,  
 3-[(3,5-Bistrifluormethylphenyl)methoxy]-2-( $\alpha$ -cyclohexylbenzyl)-1-azabicyclo[2.2.2]octan

10 und Salze davon.

4. Eine wie in irgendeinem der vorherigen Ansprüche beanspruchte Verbindung zur Verwendung in der Therapie.

15 5. Ein Verfahren zur Herstellung einer wie in irgendeinem der Ansprüche 1 bis 3 beanspruchten Verbindung, wobei das Verfahren die Umsetzung einer Verbindung der Formel (III) mit einer Verbindung der Formel (IV):



30 worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> wie für Formel (I) definiert sind und einer der Reste R<sup>30</sup> und R<sup>31</sup> eine Abgangsgruppe darstellt und der andere der Reste R<sup>30</sup> und R<sup>31</sup> OH darstellt, in Gegenwart einer Base umfaßt.

35 6. Eine pharmazeutische Zusammensetzung, die eine wie in irgendeinem der Ansprüche 1 bis 3 beanspruchte Verbindung in Verbindung mit einem pharmazeutisch annehmbaren Träger oder Hilfsstoff enthält.

7. Die Verwendung einer wie in irgendeinem der Ansprüche 1 bis 3 beanspruchten Verbindung zur Herstellung eines Medikaments zur Behandlung physiologischer Störungen, die mit einem Überschuß an Tachykininen in Verbindung stehen.

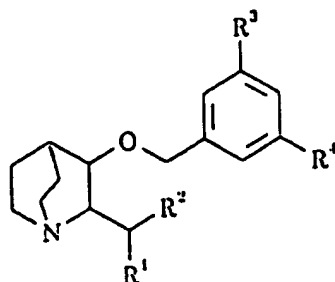
40 Revendications

1. Composé de formule (I), ou sel acceptable d'un point de vue pharmaceutique de ce dernier

45

50

55



(I)

dans laquelle

R<sup>1</sup> représente un groupe phényle non substitué ou phényl méthoxylé ;

R<sup>2</sup> représente le groupe benzyle ou cyclohexyle ; et

R<sup>3</sup> et R<sup>4</sup> représentent chacun indépendamment de l'autre un groupe méthyle ou trifluorométhyle.

2. Composé selon la revendication 1, dans lequel R<sup>3</sup> et R<sup>4</sup> sont tous les deux des groupes trifluorométhyle.

3. Composé selon la revendication 1, choisi parmi les composés suivants :

3-[(3,5-diméthylphényl)méthoxy]-2-(1,2-diphényléthyl)-1-azabicyclo[2.2.2]octane ;

3-[(3,5-bistrifluorométhylphényl)méthoxy]-2-(1,2-diphényléthyl)-1-azabicyclo[2.2.2]octane ;

3-[(3,5-bistrifluorométhylphényl)méthoxy]-2-[1-(1-(4-méthoxyphényl)-2-phényl)éthyl]-1-azabicyclo[2.2.2]octane ;

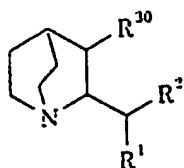
3-[(3,5-bistrifluorométhylphényl)méthoxy]-2-[1-(1-(3-méthoxyphényl)-2-phényl)éthyl]-1-azabicyclo[2.2.2]octane ;

3-[(3,5-bistrifluorométhylphényl)méthoxy]-2-(α-cyclohexylbenzyl)-1-azabicyclo[2.2.2]octane ;

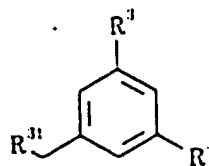
et leurs sels.

4. Composé selon l'une quelconque des revendications précédentes, pour utilisation en thérapie.

5. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 3, lequel procédé consiste à faire réagir en présence d'une base un composé de formule (III) avec un composé de formule (IV) :



(III)



(IV)

dans lesquelles R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont tels que définis pour la formule (I), et l'un des radicaux R<sup>30</sup> et R<sup>31</sup> représente un groupe éliminable et l'autre radical R<sup>30</sup> et R<sup>31</sup> représente OH.

6. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 3 en asso-

ciation avec un support ou excipient acceptable d'un point de vue pharmaceutique.

7. Utilisation d'un composé selon l'une quelconque des revendications 1 à 3 pour la fabrication d'un médicament destiné au traitement de troubles physiologiques associés à un excès de tachykinines.

5

10

---

15

20

25

30

35

40

45

50

55